

**REMARKS**

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application, in light of the above amendments and following remarks are respectfully requested.

As correctly indicated in the Office Action Summary, claims 1-87 are pending. Of these claims, 1-58 and 72-87 are withdrawn from further consideration. Applicant cancels claims 1-87 without prejudice or disclaimer, and submits new claims 88-101 for consideration.

New claims 88-101 point out more particularly and claim more distinctly the subject matter of Applicants' invention. No prohibited new matter has been introduced by this Amendment. Applicants reserve the right to pursue in a division or continuation application any subject matter canceled by way of this Amendment without prejudice or disclaimer. Applicants also submit that examination of the newly added Claims will not present any burden on the Examiner, because a prior art search of cephalotaxane derivatives with side chains had been previously performed with Claims 59-71, and the subject matter of new claims 88-101 is analogous to claims 59-71.

Support for claims 72-85 is located at least in the claims as filed and throughout the specification, particularly where Z is recited as oxygen (for example, pages 58-59).

**I. Restriction Requirement**

Applicants have canceled claims 1-58 and 72-87 in light of the Restriction Requirement which the Examiner has made final in the outstanding Official Action.

**II. Applicants' Information Disclosure Statement of June 4, 1999**

Applicants respectfully bring the Examiner's attention to the PTO-1449 form filed with the U.S. Patent and Trademark Office on June 4, 1999 and returned by the Examiner with the present Official Action. The Examiner has not initialed or otherwise marked as considered all of the references cited in the on the PTO-1449 form. Therefore, it is unclear whether or not the Examiner has considered the uninitialed references. Applicants enclose a copy of the PTO-1449 form in question, and respectfully request the Examiner to indicate whether or not all of references have been considered.

**III. Rejections under 35 U.S.C. § 112, Second Paragraph**

Claims 59-71 are rejected under 35 U.S.C. § 112, second paragraph as indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 59. Applicants have canceled claim 59 and added claim 88 in order to obviate the rejections cited below. Claim 59 was rejected as indefinite for the following reasons:

Claim 59 recited "tertiary heterocycloalkanes" when not all claimed compounds were tertiary. New claim 88 does not recite the phrase "tertiary heterocycloalkanes".

Claim 59 recited Z as nitrogen, but the valence of nitrogen is not met. New claim 88 obviates this rejection by not requiring Z to be nitrogen.

Claim 59 recited "optionally including heteroatoms", when it is not clear what heteroatoms are intended and how many heteroatoms are intended in the hydrocarbon radical. New claim 88 obviates this rejection because it does not recite the possibility of heteroatoms.

Claim 59 recited  $n=0$  in proviso 1 and 2 when the scope of claim 59 recites the value of  $n$  as 1-8. New claim 88 obviates the rejection because the claimed values for  $n$  are now 0-8, which encompass the claimed provisos.

Claim 59 recited functional groups such as "carboxymethyl, O-methyl, OH" in provisos 1-6, when these functional groups had no antecedent basis in the claimed definitions of  $R^5$ ,  $R^6$  and  $R^8$ . New claim 88 contains antecedent basis for the recited functional groups, and obviates this rejection. In addition, claim 59 recited the phrase " $R^5$  is not hydrogen; except for compounds...". The semi-colon following "hydrogen" made it unclear whether the phrase is part of the following proviso or not. New claim 88 does not include this phrase, and so the rejection is obviated.

Claim 60. Claim 60 was objected to for being in improper dependent form as it fails to further limit the subject matter of a previous claim. Applicants have canceled claim 60 in order to moot this objection.

Claims 61 and 63. Claims 61 and 63 are improper claims because they depend on claim 54, which is not part of the elected subject matter. Claims 61 and 63 have been canceled, and so this objection is mooted.

Claim 62. Claim 62 is an improper claim because it does not recite the definition of  $R^6$ ,  $R^8$  and n values. Claim 62 has been canceled, and so this objection is mooted.

Claim 66. Claim 66, as an independent claim, is improper because it does not recite the definition of  $R^5$ . Claim 66 has been canceled, and so this objection is obviated. Corresponding new claim 76 depends back to new claim 75, which defines  $R^5$ .

Claims 64, 65, 69 and 70. Claims 64, 65, 69 and 70 are rejected as indefinite because they recite harringtonic acid when the formula disclosed is not harringtonic acid. Claims 64, 65, 69 and 70 have been canceled, and so this objection is obviated.

Claims 59-71. Claims 59-71 have several typographical errors. Because claims 59-71 have been canceled, these rejections are obviated.

Accordingly, in light of the arguments and the addition of the new claims, the rejections under 35 U.S.C. §112, second paragraph, respectfully should be withdrawn.

**IV. Rejection under 35 U.S.C. § 112, First Paragraph**

Claim 59 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification. Specifically, the specification is not enabling for compounds where Z is S. Claim 59 has been canceled and replaced with new claim 88, which recites oxygen in the Z position. Accordingly, the rejection of claim 59 has been obviated.

**V. Rejections under 35 U.S.C. § 102**

For proving anticipation, "anticipation requires the presence in a single prior art disclosure of all elements of a claimed invention as arranged in the claims." Jamesbury Corp. v. Litton Industrial Products, Inc. 225 U.S.P.Q. 253, 256 (Fed. Cir. 1985). The cited references do not describe or suggest all of the elements of the rejected claims, as discussed in greater detail below.

Claim 59. Claim 59 is rejected under 35 U.S.C. § 102(b) for being anticipated by the following references:

Wasserman et al., U.S. Patent No. 4,178,286. Wasserman et al. is cited for teaching several azacycloalkane carboxylic acids, all of which contain a nitrogen atom. The disclosure of Wasserman et al. purportedly meets the instant claim limitations if it is assumed that Applicants are permitting substituents on the nitrogen. Applicants have canceled claim 59 and replaced it with new claim 88, which does

not teach a structure bearing a nitrogen atom; rather, the compound of claim 88 recites oxygen in the Z position. Accordingly, this rejection is obviated.

Ondetti et al., U.S. Patent No. 4,154,840. Ondetti et al. teaches proline derivatives, which purportedly are some of the carboxylic acid derivatives taught in claim 59. Ondetti et al. does not teach any compounds containing oxygen, while new claim 88 recites compounds comprising oxygen in the Z position. Accordingly, this rejection is obviated.

Henning et al., U.S. Patent No. 4,849,524. Henning et al. is cited for purportedly teaching a process for preparing several proline derivatives disclosed in claim 59. Again, the compounds of Henning et al. do not contain oxygen, while new claim 88 recites oxygen in the Z position. Accordingly, this rejection is obviated.

Fritz-Langhals, U.S. Patent No. 5,334,730. Fritz-Langhals is cited for purportedly teaching a process for preparing optically active carboxylic acids, which include the compounds claimed in the instant invention. Applicants respectfully note that the carboxylic acids of Fritz-Langhals, which may be tetrahydrofuran-2-carboxylic acids, do not read upon the present invention as taught in new claim 88, because claim 88 contains the proviso that R<sup>6</sup> and R<sup>8</sup> cannot be hydrogen simultaneously. Thus, the rejection is obviated.

Bosies et al., U.S. Patent No. 4,409,236. Bosies et al. is cited for purportedly teaching several N-substituted aziridine-2-carboxylic acid derivatives, which include compounds claimed herein when the reference limits X to COOH. Applicants respectfully submit that the structures taught by Bosies et al. are now outside the

scope of the present invention because they teach nitrogen, and the rejected claims of the present invention do not recite nitrogen. Further, the compounds of Bosies et al. do not contain oxygen, while new claim 88 recites oxygen in the Z position. Thus, the rejection is obviated.

Sayo et al., U.S. Patent No. 5,502,221. Sayo et al. is cited for purportedly teaching cyclohexyl substituted oxirane carboxylic acids, which include compounds claimed herein. Applicants respectfully note that the oxirane carboxylic acids of Sayo et al. do not read upon the present invention as taught in new claim 88, because claim 88 contains the proviso that R<sup>6</sup> and R<sup>8</sup> cannot be hydrogen simultaneously. The compounds taught by Sayo et al. require that R<sup>6</sup> and R<sup>8</sup> be hydrogen simultaneously. Thus, the rejection is obviated.

Claims 59-61. Claims 59-61 are rejected 35 U.S.C. § 102(b) for being anticipated by the following references:

Newman et al., Organic Reactions, Volume V, page 414-440, 1952. Newman et al. is cited for purportedly teaching a review of Darzens glycidic ester condensation which includes compounds claimed herein. Because new claim 88 recites oxygen in the Z position, the structures of Newman et al., which do not teach an oxygen containing compound, does not teach or suggest the present invention. Thus, the rejection is obviated.

Levy et al. U.S. Patent No. 2,289,339 ("Levy I"), Levy et al., U.S. Patent No. 2,889,340 ("Levy II") and Kogure et al. U.S. Patent No. 4,042,617. Levy I, Levy II

and Kogure et al. are cited for teaching several glycidic acids purportedly claimed herein. Neither of the Levy et al. patents read on the instant invention because the cited references teach only unsaturated di-alkyl substituted epoxy-acid esters, which are excluded from the instant invention. Specifically, new claim 88 excludes compounds where n is O and R<sup>5</sup> is not CH<sub>2</sub>CO<sub>2</sub>H or CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>, and so the rejection is obviated.

Kogure et al., which discloses a process for making 2-methyl substituted arylpyruvic acid compounds, does not read on the instant invention because Kogure et al. teaches that R<sup>5</sup> is never hydrogen. In claim 88 of the present invention, R<sup>5</sup> can be hydrogen. Thus, Kogure et al. in fact teaches away from the present invention, and the rejection is obviated.

Eisetter et al., U.S. Patent No. 4,430,339. Eisetter et al. is cited for purportedly teaching several substituted oxirane carboxylic acids, which include compounds claimed herein, for use in treating disturbances of glucose and fat metabolism. Eisetter et al. does not read on the present invention, because the disclosed oxirane carboxylic acids are substituted by a radical which cannot be -CH<sub>2</sub>COOH or -CH<sub>2</sub>COOCH<sub>3</sub>. The present invention claims compounds which are substituted with -CH<sub>2</sub>COOH or -CH<sub>2</sub>COOCH<sub>3</sub>. Thus, the rejection is obviated.

Mohrbacher et al., U.S. 4,132,720. Mohrbacher et al. is cited for purportedly teaching several alkenyl substituted oxirane carboxylic acids, which include compounds claimed herein, for use as hypoglycemic agents. Mohrbacher et al. does not read on the present invention, because the disclosed oxirane carboxylic



acids are substituted by an alkenyl which cannot be  $-\text{CH}_2\text{COOH}$  or  $-\text{CH}_2\text{COOCH}_3$ .

The present invention claims compounds which are substituted with  $-\text{CH}_2\text{COOH}$  or  $-\text{CH}_2\text{COOCH}_3$ . Thus, the rejection is obviated.

Delay, U.S. Patent No. 4,252,728. Delay is cited for purportedly teaching several norborane substituted oxirane carboxylic acids, which include compounds claimed herein, for use as perfumes. The oxirane carboxylic acids taught by Delay are outside the scope of the present invention because they are substituted by norborane, which is not recited by the rejected claims. Thus, Delay in fact teaches away from the present invention, and the rejection is obviated.

Eiter et al., U.S. Patent No. 3,246,038. Eiter et al. is cited for purportedly teaching cycloalkenyl substituted oxirane carboxylic acids, which include compounds claimed herein. As above, the oxirane carboxylic acids taught by Eiter et al. are outside the scope of the present invention because they are substituted by norborane, which is not recited by the rejected claims. Thus, Eiter et al. in fact teaches away from the present invention, and the rejection is obviated.

Leroux, Bulletin De La Societe Chimique France 344-350. Leroux is cited for purportedly teaching several tetrahydrofuranyl and tetrahydropyranyl carboxylic acids which purportedly include those claimed herein. Applicants respectfully note that the carboxylic acids of Leroux do not read upon the present invention as taught in new claim 88, because claim 88 contains the proviso that  $\text{R}^6$  and  $\text{R}^8$  cannot be hydrogen simultaneously. The compounds taught by Leroux require that  $\text{R}^6$  and  $\text{R}^8$  be hydrogen simultaneously. Thus, the rejection is obviated.

Nagai et al., Tetrahedron Letters, 40, 4797-4801, 1966. Nagai et al. is cited for purportedly teaching a process for making a pyran carboxylic acid which the Examiner argues is generically claimed hereon. Under new claim 88, the pyran carboxylic acids taught by Nagai et al., which do not have an oxygen at the corresponding Z position, are no longer under the scope of the present invention. Thus, the rejection is obviated.

Iskura Sangyo Co., Japanese Patent No. 58032880. Iskura Sangyo Co. is cited for purportedly teaching tetrahydrofuran carboxylic acid which the Examiner argues is generically claimed hereon. Applicants respectfully note that the tetrahydrofuran carboxylic acids of Iskura Sangyo do not read upon the present invention as taught in new claim 88, because claim 88 contains the proviso that R<sup>6</sup> and R<sup>8</sup> cannot be hydrogen simultaneously. The compounds taught by Iskura Sangyo require that R<sup>6</sup> and R<sup>8</sup> be hydrogen simultaneously. Thus, the rejection is obviated.

Hiranuma et al., J. Org. Chem. 48, 5321-5326, 1983. Applicants respectfully note that the Examiner's reasons for citing Hiranuma et al. are vague. The Examiner directs Applicants to a page disclosing a compound and a page disclosing the "process of making", but provides no other guidance as to how Hiranuma et al. reads on the present invention. In any case, Hiranuma et al. teaches dihydropyranic acid, which is completely outside the scope of the present invention. Thus, this rejection is obviated.

Claims 59-65. Claims 59-65 are rejected under 35 U.S.C. § 102(b) for being anticipated by the following reference:

Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica) 27, 178-184, 1992.

Wang et al. is cited for purportedly teaching compounds 8 and 9 which bear the tetrahydrofuran and tetrahydropyran carboxylic acid claimed herein. The compounds of Wang et al. do not read upon the present invention as taught in new claim 88, because claim 88 contains the proviso that R<sup>6</sup> and R<sup>8</sup> cannot be hydrogen simultaneously. The Examiner also notes that it is held that Wang et al. inherently teaches these acids for cephalotaxine alkaloids. *In re Petering et al.* 133 USPQ 275; *In Re Schaumann*, 195 USPQ 5. As stated above, this rejection is obviated because claim 88 does not recite cephalotaxine alkaloids.

Claim 59. Claim 59 is rejected under 35 U.S.C. 102(e) for being anticipated by the following references:

Russo-Rodriguez et al., U.S. Patent No. 6,107,291. Russo-Rodriguez et al. is cited for purportedly teaching azepine or larger medium ring carboxylic acid, which includes compounds claimed herein as intermediates for making anti-inflammatory agents and other pharmaceuticals. Applicants respectfully submit that the structures taught by Russo-Rodriguez et al. are now outside the scope of the present invention because they require a nitrogen substituted ring, and the rejected claims and new claims of the present invention do not recite nitrogen. Thus, the rejection is obviated.

Kalish et al., U.S. Patent No. 5,834,467. Kalish et al. is cited for purportedly teaching HIV protease inhibitors which include compounds claimed herein as intermediates. As above, Applicants respectfully submit that the structures taught by Kalish et al. are now outside the scope of the present invention because they teach nitrogen substituted rings and chains, and the rejected claims of the present invention do not recite nitrogen. Thus, the rejection is obviated.

Accordingly, in light of the arguments and the addition of the new claims discussed above, the rejections respectfully should be withdrawn.

**VI. Rejections under 35 U.S.C. § 103**

Claims 59-65. Claims 59-65 are rejected under 35 U.S.C. § 103(a) for being unpatentable over the references discussed below.

To make a *prima facie* case of obviousness, the Federal Circuit has articulated the analysis of a proper analysis under 35 U.S.C. § 103 as follows:

[W]here claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis under § 103 requires, inter alia, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. See In re Dow Chemical Co., 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure.

In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced, because the art cited by the Examiner, alone or in combination, does not suggest that the methods claimed, let alone that the claimed methods could be conducted with a reasonable expectation of success.

Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica) 27, 178-184, 1992 ("Wang I"). Claims 59-65 are rejected as unpatentable over Wang I in view of Wang et al. Yaoxue Xuebao (Acta. Pharm. Sinica) 27, 173-177, 1992 ("Wang II"). Wang I is cited for purportedly teaching the tetrahydrofuran and tetrahydropyran esters of cephalotaxine as noted in the above § 102 rejection. Wang II is cited for purportedly teaching a process for cyclizing the open chain acid, i.e. compound 7, as bearing a cephalotaxyl (CTX) group to the corresponding tetrahydrofuran compound.

Huang et al., the Alkaloids, Vol. XXII 157-224, 1984. Claims 59-65 are rejected as unpatentable over Huang et al., the Alkaloids, Vol. XXII 157-224, 1984 in view of Wang II. Huang et al. is cited for purportedly teaching the process for hydrolyzing the cephalotaxine alkaloids and the synthesis of the acid components. Wang II is cited for purportedly teaching a process for cyclizing the open chain acid ie compound 7 as bearing a CTX group to the corresponding tetrahydrofuran compound.

The present invention teaches the process of esterfying the hindered free alcohol of either a cephalotaxine or the corresponding metal alkoxide using a substituted tertiary caboxylic oxacycloalkane acid. The cephalotaxine is esterfied using the keto alkanoyl chloride of formula 7, which lacks the end hydroxyl and does not contain the secondary chain by the tertiary carboxyl , and result in formula 8. This process is performed in its entirety, both in terms of the skeleton and the functionalization, and permits one practicing the claimed invention to directly produce the harringtonines.

The Examiner argues that the starting materials of Wang I, Wang II and Huang are analogous to the formula 7 of the claimed invention, with a methoxy on the tertiary carboxylic group. Applicants respectfully submit that this is not the case. The starting materials of the instant invention are different from those of the cited reference in that they confer an additional benefit. The claimed process of the present invention results in enantiomerically pure herringtonines, even from racemic cephalotaxine, because the asymmetric center on this side chain in created prior to the esterfication step. The creation of the side chain prior to esterfication results in a side chain precursor that is enantiomerically pure before being attached. These diastereoisomers obtained from racemic cephalotaxine can be separated using chromatograhpy.

Accordingly, the cited art of Wang I, Wang II and Huang, alone or in combination, do not suggest that the claimed invention could be conducted with a reasonable expectationn of success. In fact, the process of the claimed invention

results in a different product from the compounds of the cited art (enantimerically pure herringtonines). Applicants respectfully request the appropriate withdrawal of the rejection.

Claim 59. Claim 59 stands rejected in view of Wasserman et al., Ondetti et al., Henning et al. or Bosies et al. (alone, rather than in combination).

Wasserman et al., U.S. Patent No. 4,178,286. Wasserman et al is cited for purportedly teaching several azacycloalkane carboxylic acids claimed herein as intermediates same as the utility of instant invention. The Examiner argues that Wasserman et al. teaches a process for making higher ring size azacycloalkane and teaches equivalency of the exemplified 4-membered ring with those disclosed in the definition of n.

Ondetti et al., U.S. Patent No. 4,154,840. The Examiner does not give any reason for the rejection of claim 59 under 35 U.S.C. § 103 over Ondetti et al. However, upon review of the cited reference, Applicants respectfully submit that claim 59 is not obvious over Ondetti et al. for reasons discussed below.

Henning et al., U.S. Patent No. 4,849,524. Henning et al. was cited for teaching processes for preparing several proline derivatives purportedly claimed herein as intermediates for preparing inhibitors of angiotensin converting enzymes.

Bosies et al., U.S. Patent No. 4,409,236. Bosies et al. is cited for purportedly teaching several N-substituted aziridine-2-carboxylic acid derivatives which purportedly include compounds claimed herein from immuno-stimulation.

With regards to the above separate rejections of claim 59 over Wasserman et al., Ondetti et al., Henning et al. and Bosies et al., Applicants respectfully draw the Examiner's attention to new claim 88. Following the entry of claim 88, the present invention will recite compounds bearing an oxygen in the Z position. As a result, the compounds of the cited art are not only outside the scope of the present invention, but in fact teach away from the claims of the present invention. The compounds of the cited art do not teach structures with an oxygen in the corresponding Z position, while the claims of the present invention recite only oxygen in the Z position. In addition with regard to Wasserman et al. and Bosies et al., the cited art teach nitrogen substituted structures, while the claims of the present invention do not recite nitrogen. The Examiner's arguments are based upon the premise that the compounds recited in the rejected claims are basically the same and can be expected to have the same uses as the compounds in the cited art. This is no longer the case. Applicants respectfully request the appropriate withdrawal of the rejection.

#### **CONCLUSION**

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.



In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions to that prosecution of this application may be expedited.

Respectfully submitted,

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